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Management of Patients Undergoing CAR-T Cell Therapy in Germany

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Abstract

Introduction: Chimeric antigen receptor positive T cell (CAR-T cell) treatment became standard therapy for relapsed or refractory hematologic malignancies, such as non-Hodgkin's lymphoma and multiple myeloma. Owing to the rapidly progressing field of CAR-T cell therapy and the lack of generally accepted treatment guidelines, we hypothesized significant differences between centers in the prevention, diagnosis, and management of short- and long-term complications. ***Methods:*** To capture the current CAR-T cell management among German centers to determine the medical need and specific areas for future clinical research, the DAG-HSZT (Deutsche Arbeitsgemeinschaft für Hämatopoetische Stammzelltransplantation und Zelluläre Therapie; German Working Group for Hematopoietic Stem Cell Transplantation and Cellular Therapy) performed a survey among 26 German CAR-T cell centers. ***Results:*** We received answers from 17 centers (65%). The survey documents the relevance of evidence in the CAR-T cell field with a

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homogeneity of practice in areas with existing clinical evidence. In contrast, in areas with no – or low quality – clinical evidence, we identified significant variety in management in between the centers: management of cytokine release syndrome, immune effector cell-related neurotoxicity syndrome, IgG substitution, autologous stem cell backups, anti-infective prophylaxis, and vaccinations. ***Conclusion:*** The results indicate the urgent need for better harmonization of supportive care in CAR-T cell therapies including clinical research to improve clinical outcome.

Introduction

Cellular therapies including chimeric antigen receptor positive T cell (CAR-T cell) treatment represent a rapidly progressing field with new therapeutic options entering clinical routine, with CAR-T cells targeting CD19 (lymphomas, leukemias) or BCMA (multiple myeloma) already becoming standard treatment for relapsed or refractory hematologic malignancies [1–9]. Table 1 shows the products approved in Europe and their respective indications. In addition, numerous studies are underway in other tumor entities, which suggest that CAR-T cells with different antigen specificities will be used more widely in the near future.

Although effective even in advanced lines of treatment, short- and long-term side effects can be substantial, requiring supportive care which is currently applied mainly based on expert knowledge and small clinical trials, resulting in significant differences in the prevention, diagnosis, and management of patients undergoing CAR-T cell therapy. Specifically, in the areas of cytokine release syndrome (CRS), immune effector cell-related neurotoxicity syndrome (ICANS), IgG substitution, autologous hematopoietic stem cell administration, and anti-infective prophylaxis, there is no consensus on supportive care of patients. To document the current supportive care of short- and long-term complications associated with CAR-T cell therapy in Germany and subsequently determine the medical need and specific areas for future clinical research, we performed a survey among 26 German CAR-T Centers.

Methods

We designed questions as well as answer choices (O.P. and D.W.) and discussed/edited them together with the co-authors P.D., M.S., W.B. The questions and the respective choices of answers are provided in Tables 2–7. The DAG-HSZT (Deutsche Arbeitsgemeinschaft für Hämatopoetische Stammzell-transplantation und Zelluläre Therapie e. V.; German Working Group for Hematopoietic Stem Cell Transplantation and Cellular Therapy) then designed an online survey in Survey Monkey: https://de.surveymonkey.com and distributed the survey among the PIs from all 26 German CAR-T cell centers.

Results

Twenty senior physicians from 17 out of 26 CAR-T centers in Germany completed the online survey. The results are presented according to the topics CAR-T cell logistics, complication management (CRS, ICANS, and cytopenia), infections, and vaccination.

CAR-T Cell Logistics

We were specifically interested in where patient care takes place before, during, and after CAR-T cell administration (Table 2). Roughly half of CAR-T cell centers administer lymphodepletion as well as the infusion of CAR-T cells on intermediate care wards. In approximately 15% of centers, patient-, CAR-T-, as well as disease-related factors play a role in the decision whether to administer CAR-T on a regular ward or on an intermediate care ward.

The majority of centers discharge patients without severe complications from the hospital after day +10 post-CAR-T infusion. Around 40% of patients routinely discharge after day +14 post-CAR-T administration. After hospital discharge, accreditation requirements necessitate providing care for patients exclusively at the CAR-T centers during the first months after CAR-T cell treatment. Following the initial first month, roughly one-quarter of the centers continued outpatient evaluations exclusively by the CAR-T cell center. In 6% of the centers, patients are subsequently exclusively managed by the referring institution, while the majority of centers shared responsibility between the referring physicians and the CAR-T cell center.

CRS Management

We were mainly interested in the pharmacologic management of CRS because we identified this as an area of broad variability of clinical care (Table 3). We first asked if, despite a very likely diagnosis of CRS, broad-spectrum antibiotics are always administered which is practiced in roughly 2/3 of responding centers. The time from CAR-T infusion to onset of CRS, the presence of co-morbidities as well as CRS grading were the most important factors in the decision to start first-line treatment with tocilizumab as well as second-line treatment with steroids. The type of CAR-T cell product used was considered less important for CRS therapy decisions by the majority of centers.

Anakinra is the third-line CRS therapy of choice in the great majority of centers (~90%). However, the dosages used are variable: 2/3 of centers use 100–200 mg/day, which is the approved dose for rheumatoid arthritis. 1/3 of centers use 300–1,000 mg anakinra/day, which is also

Table 1. Approved CAR-T cell therapies in Europe

Substance (abbreviation), manufacturer	Product name	Antigen	Approved indications (lines of therapy)
Tisagenlecleucel (Tisa-Cel), Novartis	Kymriah	CD19	Acute lymphoblastic leukemia in patients ≤25 years (3rd line or after allogeneic stem cell transplantation) Diffuse large-cell B-cell lymphoma (≥3rd line) Follicular lymphoma (≥3rd line)
Axicabtagene ciloleucel (Axi-Cel), Kite/Gilead	YesCAR-Ta	CD19	Diffuse large-cell B-cell lymphoma, high grade B-cell lymphoma (2nd line, only in case of relapse after 1st line <12 months) Diffuse large-cell B-cell lymphoma, primary mediastinal large B-cell lymphoma (≥3rd line) Follicular lymphoma (≥4th line)
Lisocabtagene maraleucel (Liso-Cel), BMS	Breyanzi	CD19	Diffuse large-cell B-cell lymphoma, high grade B-cell lymphoma, follicular lymphoma grade IIIB (2nd line, only in case of relapse after 1st line <12 months) Diffuse large-cell B-cell lymphoma, primary mediastinal B-cell lymphoma (≥3rd line) Follicular lymphoma grade IIIB (≥3rd line)
Brexucabtagene autoleucel (Brexu-Cel), Kite/Gilead	TeCAR-Tus	CD19	Acute lymphoblastic leukemia in patients ≥26 years (≥2nd line) Mantle cell lymphoma (≥2nd line after treatment with BTK-inhibitor)
Idecabtagene vicleucel (Ide-Cel), BMS	Abecma	BCMA	Multiple myeloma (≥4th line after treatment with immunomodulatory agent, proteasome inhibitor and anti-CD38)
Ciltacabtagene autoleucel (Cilta-Cel), Janssen	Carvykti	BCMA	Multiple myeloma (≥4th line after treatment with immunomodulatory agent, proteasome inhibitor and anti-CD38)

Table 2. Survey results regarding logistics of CAR-T cell therapy

Questions and answer choices	Percentage of answers selected
In which type of ward is lymphodepletion administered?	
A – Usually on intermediate care ward	50
B – Usually on regular ward	35
C – Usually in the outpatient setting	5
D – Depends on the type of CAR-T product	0
E – Depends on patient-related as well as disease-related factors	10
Do you administer CAR-T cells on normal wards?	
A – Yes, always	28
B – Sometimes, mainly dependent on CAR-T product	6
C – Sometimes, mainly dependent on patient-related as well as disease-related factors	11
D – Never, always on intermediate care ward	55
When are patients usually discharged from the hospital without serious complications?	
A – Before day +8 after CAR-T infusion	0
B – Between day +8 and +10 after CAR-T infusion	11
C – Between day +11 and +14 after CAR-T infusion	44
D – Later than day +14 after CAR-T infusion	39
E – Product-specific discharge time point	11
Where does patient care take place after the first 4 weeks?	
A – From month 2, care is usually only provided at the CAR center	24
B – From month 2 onward, care is usually only provided by the referring institution	6
C – From month 2, care is usually provided by the CAR center and the referring institution together	71

Table 3. Survey results regarding management of CRS

Questions and answer choices	Percentage of answers selected	
Do you still use therapeutic intravenous broad-spectrum antibiotics in patients with fever in the early phase after CAR-T cell therapy and a very likely diagnosis of CRS?		
A – Never	0	
B – Always	67	
C – Yes, when risk of infection is increased (e.g., cytopenia)	28	
D – Yes, only when it is severe CRS	0	
E – Yes, if risk of infection is increased or if it is severe CRS	11	
F – Yes, due to other reasons	11	
Which statements are correct regarding your CRS management with tocilizumab?	Yes	No
A – The time from CAR-T cell infusion till onset of CRS is the main factor for my decision to initiate tocilizumab treatment	44	56
B – The type of CAR-T cell product is the main factor for my decision to initiate tocilizumab treatment	11	89
C – Presence of co-morbidities is the main factor for my decision to initiate tocilizumab treatment	44	56
D – Another factor is very important for my decision to initiate tocilizumab treatment	37	63
Which statements are correct regarding your CRS management with steroids?	Yes	No
A – The time from CAR-T cell infusion till onset of CRS is the main factor for my decision to initiate steroid treatment	33	67
B – The type of CAR-T cell product is the main factor for my decision to initiate steroid treatment	17	83
C – Presence of co-morbidities is the main factor for my decision to initiate steroid treatment	39	61
D – Another factor is very important for my decision to initiate steroid treatment	33	67
Which statements are correct regarding your CRS management with other substances (beyond tocilizumab and steroids)?	Yes	No
A – I always wait for the therapeutic effectiveness of steroids before using another substance (e.g., anakinra)	72	28
B – In the case of very severe CRS, I usually use a third substance directly with the steroid (and do not wait to see if the steroids work)	17	83
Which substance/strategy is the primary standard in your center for the treatment of severe CRS when there is no improvement after tocilizumab and steroids?		
A – I am not using alternative strategies in addition to tocilizumab and steroids	0	
B – Anakinra	89	
C – Alternative IL-6 antibody	33	
D – Cytokine absorption	11	
E – Other	0	
What is the standard daily dose of anakinra in your center for the treatment of severe CRS?		
A – 100 mg–200 mg/day	67	
B – 300 mg–1,000 mg/day	33	

recommended for more acute and severe inflammatory diseases, such as cryopyrin-associated periodic syndrome (CAPS) [10].

ICANS Management

We first asked for the diagnostic workup in case ICANS was suspected (Table 4). More than 80% of centers perform magnetic resonance imaging (MRI), 2/3 request an EEG and approximately 50% do a cerebrospinal fluid puncture to determine routine parameters. Anakinra is the drug of choice for patients who are refractory to steroids in most centers (65%). Similar to CRS management with anakinra, the dosages used are variable. Popular alternative options for treatment of steroid-refractory ICANS are intrathecal chemotherapy and the use of IL-6 antibodies. Interestingly, ~25% of centers administer a combination therapy of steroids + another substance as first-line therapy for very severe ICANS.

Cytopenia Management

In patients without available stem cell backup (previously collected CD34+ autologous stem cells), 1/3 of centers are considering collecting a backup in patients at high risk for prolonged cytopenia (Table 5). Roughly 80% of centers are infusing stem cell backup's in patients with severe CAR-T cell-associated prolonged cytopenia. However, there is no consensus on the ideal time point for stem cell administration in this situation. ~45%

Table 4. Survey results regarding management of ICANS

Questions and answer choices	Percentage of answers selected	
Which statements are correct regarding your diagnostic ICANS (neurotoxicity) management?	Yes	No
A – ICANS is a clinical diagnosis and I do not initiate any further diagnostics (MRT, EEG, cerebrospinal fluid puncture) in the case of typical manifestations	28	72
B – I usually request an MRI if an ICANS is present	83	17
C – I usually request an EEG if an ICANS is present	67	33
D – In case of an ICANS I usually do a cerebrospinal fluid puncture to determine routine parameters (cell count, protein)	56	44
E – In case of an ICANS, I usually do a CSF puncture to quantify CAR-T cells	22	78
Which statements are correct regarding your ICANS management with other substances (beyond steroids)?	Yes	No
A – I always wait for the therapeutic effectiveness of steroids before using another substance (e.g., anakinra)	78	22
B – In the case of very severe CRS, I usually use a third substance directly with the steroid (and do not wait to see if the steroids work)	24	76
Which substance/strategy is the primary standard in your center for the treatment of severe ICANS when there is no improvement after steroids?		
A – I am not using other drugs/strategies than steroids	18	
B – Anakinra	65	
C – Alternative IL-6 antibody	18	
D – Intrathekal chemotherapy	24	
E – Other	0	
What is the standard daily dose of anakinra in your center for the treatment of severe ICANS?		
A – 100 mg–200 mg/day	63	
B – 300 mg–1,000 mg/day	37	

Table 5. Survey results regarding management of cytopenia

Questions and answer choices	Percentage of answers selected	
Do you collect autologous stem cell transplantation as a backup prior to CAR-T cell therapy (when there are no backups from a previous or planned autoSCT)?		
A – Never	67	
B – Always	0	
C – Yes, when risk of prolonged cytopenia is increased	33	
Which statement is most accurate regarding your management of giving autologous stem cell transplants (if available) when patients have severe post-CAR-T hematotoxicity?		
A – In case of severe CAR-T-associated cytopenia I administer autoSCT usually before day +15 after CAR-T infusion	13	
B – In case of severe CAR-T-associated cytopenia I administer autoSCT usually between day +16 and day +45 after CAR-T cell infusion	44	
C – I'll wait for a spontaneous improvement first and then, if necessary, transfuse an autoSCT after day +45 after CAR-T cell infusion	25	
D – I do not administer autoSCT, even with severe hematotoxicity	19	
Which statements are correct regarding administration of G-CSF when patients have severe neutropenia after CAR-T?	Yes	No
A – I administer G-CSF in patients with neutrophils <1,000\µL	13	87
B – I administer G-CSF in patients with neutrophils <500\µL	63	37
C – I administer G-CSF in patients with neutrophils <200\µL	78	22
D – I do not administer G-CSF in this situation	0	100
E – I do not administer G-CSF in the early phase after CAR-T because of the CRS/ICANS risk. However, later use is conceivable	69	31
Which statements are correct regarding your management of the administration of Aspergillus-effective antimycotics if patients have severe neutropenia after CAR-T?		
A – I administer anti-fungal prophylaxis in patients with neutrophils <1,000\µL	18	82
B – I administer anti-fungal prophylaxis in patients with neutrophils <500\µL	71	29
C – I administer anti-fungal prophylaxis in patients with neutrophils <200\µL	53	47
D – I generally do not use anti-fungal prophylaxis in this situation	13	87

Table 6. Survey results regarding prophylaxis of infections

Questions and answer choices	Percentage of answers selected	
Do you use broad-spectrum antibiotics prophylactically after CAR-T cell therapy (PCP prophylaxis is not meant here)?		
A – Never	35	
B – Always	0	
C – Yes, if cytopenia risk is increased	10	
D – Yes, if neutrophils <500/µL	45	
E – Yes, if neutrophils <200/µL	10	
F – Yes, at fixed times	0	
G – Yes, only with non-resorbable antibiotics	5	
Do you use prophylactic antimycotics after CAR-T cell therapy to prevent invasive aspergillosis?		
A – Never	26	
B – Always	16	
C – Yes, if cytopenia risk is increased	16	
D – Yes, if neutrophils <500/µL	32	
E – Yes, if neutrophils <200/µL	5	
F – Yes, due to other reasons	16	
Do you regularly use VZV prophylaxis (e.g., aciclovir/valaciclovir) after CAR-T cell therapy?		
A – Never	5	
B – Yes, till 3 months after CAR-T therapy	15	
C – Yes, till 6 months after CAR-T therapy	30	
D – Yes, till 9 months after CAR-T therapy	0	
E – Yes, till 12 months after CAR-T therapy	5	
F – Yes, dependent on other factors	60	
Do you regularly use PCP prophylaxis (e.g., Cotrim) after CAR-T cell therapy?		
A – Never	5	
B – Yes, till 3 months after CAR-T therapy	15	
C – Yes, till 6 months after CAR-T therapy	30	
D – Yes, till 9 months after CAR-T therapy	0	
E – Yes, till 12 months after CAR-T therapy	5	
F – Yes, dependent on other factors	60	
Which statements are correct regarding your management of immunoglobulin G (IgG) deficiency in asymptomatic patients (patients without a tendency to infection or infection)?	Yes	No
A – I never substitute IgG in asymptomatic patients after CAR-T	19	81
B – I substitute IgG in asymptomatic patients at levels <4 g/L	60	40
C – I only substitute IgG in asymptomatic patients at levels <3 g/L	14	86
D – I only substitute IgG in asymptomatic patients at levels <2 g/L	27	73
E – I only substitute IgG in asymptomatic patients at levels <1 g/L	14	86
Which statements are correct regarding your management of immunoglobulin G (IgG) deficiency and infections or susceptibility to infections?	Yes	No
A – I never substitute IgG for severe infections after CAR-T	0	100
B – In severe infections after CAR-T I substitute IgG at levels <4 g/L	100	0
C – In severe infections after CAR-T I only substitute IgG at levels <3 g/L	14	86
D – In severe infections after CAR-T I only substitute IgG at levels <2 g/L	14	86
E – In severe infections after CAR-T I only substitute IgG at levels <1 g/L	14	86

administer a stem cell backup between day +16 and day +45 after CAR-T cell infusion. ~15% consider administration before day +15 and 25% believe that the best time point is after day +45.

We found a high level of agreement that granulocyte colony-stimulating factor (G-CSF) should be used in patients with severe neutropenia after CAR-T cell therapy (100%), but again, there is no consensus regarding timing and the severity of neutropenia as triggers for G-CSF. The majority of centers consider an aspergillus-effective antifungal prophylaxis in patients with severe CAR-T cell-related neutropenia.

Prophylaxis of Infectious Complications Including Vaccination

Aciclovir prophylaxis is applied by all but 1 center with considerable variability, with regard to length with 6 (30%) centers applying prophylaxis for 6 months, 3 (15%) only for 3 months, and 12 (60%) adapting the duration to T-cell regeneration, among other risk factors. The use of pneumocystis jirovecii prophylaxis followed the identical pattern with almost exclusive use of cotrimoxazole (Table 5–7).

IgG substitution showed even higher variability, with a significant proportion performing substitution already in asymptomatic patients: <IgG 4 g/L in 9

Table 7. Survey results regarding vaccinations

Questions and answer choices	Percentage of answers selected	
Which statements are correct regarding your management when carrying out a basic immunization after CAR-T again?	Yes	No
A – Early basic immunization starting around day +90 or earlier is a good strategy	8	92
B – Basic immunization should start around 6 months after CAR-T infusion	64	36
C – Basic immunization should start around 9 months after CAR-T infusion	0	100
D – Basic immunization should start around 12 months after CAR-T infusion	0	100
E – Basic immunization should only be carried out after recovery of B cells in peripheral blood independent from a fixed time point	31	69
F – I do not recommend basic immunization after CAR-T therapy	27	73
Which statements are correct regarding your management when carrying out a SARS-CoV-2 vaccination after CAR-T?	Yes	No
A – Early SARS-CoV-2 vaccination around day +90 or earlier is a good strategy	40	60
B – SARS-CoV-2 vaccination should be started 4–6 months after CAR-T infusion	50	50
C – SARS-CoV-2 vaccination should be started later than 6 months after CAR-T infusion	8	92
D – SARS-CoV-2 vaccination should be started only after regeneration of B cells	21	79
E – I do not recommend refreshing SARS-CoV-2 vaccination after CAR-T	0	100
F – I use passive immunization with Evusheld before patients get vaccinated	69	31

(60%) centers, <IgG 3 g/L in 2 (14%), IgG <2 g/L in 4 (26%) centers, and IgG <1 g/L in 2 (14%) centers, while only 3 centers would never substitute immunoglobulins in asymptomatic patients (applying to the EMA guidelines [11]. The substitution rate significantly increased in patients with infectious complications with basically all centers using substitution of immunoglobulins if serum levels were < 4 g/dL, although some centers also occasionally used lower thresholds. The vast majority of center used the IV route for substitution of immunoglobulins, with only 2 centers preferring subcutaneous application. Most of centers stop substitution of immunoglobulins after stabilization of IgG levels. Moreover, B-cell recovery is considered a decision factor to terminate substitution of immunoglobulins in 8 (75%) of the responding centers.

Revaccination after CAR-T cell therapy is considered by the vast majority of centers (72%). Most of the centers (64%) start vaccination 6 months after treatment with half of the centers integrating B-cell recovery into the decision to initiate revaccination after 6 months. Serological vaccination response is assessed for COVID-19 (50%), tetanus (47%), hepatitis B (40%), and diphtheria (40%), while other components are less frequently analyzed. Of note, influenza vaccination response was not assessed by any center. With regard to COVID-19 vaccination, 40% of the centers would already start at day 90 after CAR-T cell therapy, and an additional 50% would start between 4 and 6 months. Only 21% of the replying centers would consider depending on COVID-19 vaccination on B-cell recovery.

Discussion

In this survey performed among German CAR-T cell centers, we found a considerable variety in the practice patterns of supportive care. This reflects the absence of generally accepted treatment guidelines as well as the lack of extensive clinical data from the relatively small clinical trials leading to approval of the CAR-T cell products.

CAR-T Cell Logistics

Initially, treatment of patients undergoing CAR-T cell therapy on intermediate care wards was mandatory in Germany. Later on, the requirements were downgraded, and it is now possible to treat patients on regular wards. However, outpatient treatment during CAR-T cell infusion and in the early phase after CAR-T administration is currently not reimbursed in the German health care setting. Our survey reflects the current changes in requirements for CAR-T-cell therapy, with roughly 50% of centers still providing inpatient care on intermediate care wards versus the other half of centers already moving to regular wards. Along the same line, the duration of hospital stay is currently quite different depending on the CAR-T center in Germany. For the future, it will be important to lay the structural and regulatory basis for early discharge and for outpatient CAR-T treatment, which has been successfully used in the USA and other countries [12].

CRS and ICANS Management

Tocilizumab and steroids are approved therapeutic options in the management of CRS, while ICANS is primarily treated with steroids according to international

guidelines [13]. Our current survey demonstrates a variety of open questions ranging from diagnostic procedures to pharmacological treatment. One of the open areas in both CRS as well as ICANS is the management of steroid-refractory cases and very severe forms of CRS/ICANS.

Interestingly, anakinra is currently the standard of care in most German CAR-T cell centers in the latter situation, with variable dosing. While most centers apply relatively low doses (100–200 mg/day) according to approved treatment for rheumatoid arthritis[10], some centers use higher doses, probably as a reaction on reports that higher doses are needed for effective treatment of severe CRS/ICANS [14], and multicenter real-world and clinical trial data are required to determine the optimal dosing schedule of anakinra in this setting.

Cytopenia Management

Cytopenia is considered to be one major complication of CAR-T cell therapy. However, the definitions of severe cytopenia or prolonged cytopenia used are heterogeneous, and so far, patient populations and CAR-T products studied have been inconsistent, making it difficult to establish evidence-based standardized treatment algorithms [15–17]. When available, the majority of centers are administering stem cell boosts to patients with severe cytopenia after CAR-T cell therapy, but the optimal timing remains to be determined [18, 19]. On the other hand, only a minority of centers are collecting hematopoietic stem cell boosts prior to CAR-T cell therapy, probably reflecting logistic challenges including reimbursement and storage capacity issues.

Prophylaxis of Infectious Complications

While basically all centers perform VZV and PCP prophylaxis according to national guidelines, the length of prophylaxis varies considerably owing to the fact that outside the HIV setting, controlled data on the correlation of T cell recovery and risk for reactivation/infection are lacking.

Also, the practice of immunoglobulin substitution varies considerably. While basically all centers agree on the need for immunoglobulin replacement in the presence of infectious complications and low immunoglobulins, the substitution in asymptomatic patients (formally off label) [11] varies considerably. However, substitution of asyptomatic patients can be justified by the fact that a significant proportion of patients, especially after BCMA-directed CAR-T cell treatment, have a qualitative humoral immunodeficiency due to depletion of plasma cells, which has also been reported in extensively pre-treated B-cell lymphoma patients [20, 21]. Moreover, real-world data show late treatment-related mortality in survivors after CAR-T cell treatment, most likely due to infectious complications [3, 22]. Controlled trials evaluating an interventional versus pre-emptive approach to immunoglobulin replacement in the latter situation are urgently needed.

Since CD19 (and BCMA)-directed treatment depletes B memory (and plasma cells), protection from prior vaccination is reduced if not depleted. In consequence, patients after CAR-T cell therapy require revaccination analogous to autologous hematopoietic stem cell transplantation (autoHSCT) which is practiced in most of the CAR-T cell centers. However, the time schedule and assessment of vaccination response vary considerably, and cellular recovery is only taken into account by selected centers. Data from allogeneic HSCT indicate a relationship between cellular regeneration, production of immunoglobulins, and vaccination response, but prospective data in the CAR-T cell setting are lacking, explaining the variation of clinical practice [23, 24]. Of note, for COVID-19 and influenza vaccination, at least partial protection has been also documented by T-cell memory responses justifying early vaccination in the absence of B cells which is practiced by almost all participating centers [25–27].

In summary, our survey impressively documents the relevance of evidence with large homogeneity of practice in the presence of evidence and varying patterns in areas of a lack of prospective trials potentially impairing treatment success including early and late treatment-related mortality. This clearly calls for prospective trials not only developing and evaluating new CAR-T cell therapies but also integrating concepts to establish evidence for supportive care.

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Statement of Ethics

An ethics approval was not required because this was a questionnaire not asking questions that could identify individual patients. An exemption from requiring ethics approval was confirmed by the Ethics Committee of the University of Regensburg on September 6th, 2023.

Conflict of Interest Statement

O.P. has received honoraria or travel support from Gilead, Jazz, MSD, Novartis, Pfizer, and Therakos. He has received research support from Incyte and Priothera. He is a member of the advisory

boards for Equillium Bio, Jazz, Gilead, Novartis, MSD, Omeros, Priothera, Sanofi, Shionogi, and SOBI. D.W. received honoraria from Novartis, Gilead, BMS, Takeda, and Behring and received research support from Novartis. MJ has received honoraria or travel support from Novartis, BMS, Pfizer, and Jazz. BvT is an advisor or consultant for Allogene, BMS/Celgene, Cerus, Incyte, IQVIA, Gilead Kite, Miltenyi, Novartis, Noscendo, Pentixapharm, Roche, Amgen, Pfizer, Takeda, Merck Sharp & Dohme, and Gilead Kite; has received honoraria from AstraZeneca, BMS, Incyte, Novartis, Roche Pharma AG, Takeda, and Merck Sharp & Dohme; reports research funding from Novartis (Inst), Merck Sharp & Dohme (Inst), and Takeda (Inst); and reports travel support from AbbVie, AstraZeneca, Gilead Kite, Merck Sharp & Dohme, Roche, Takeda, and Novartis. GB has received honoraria from Novartis, Jazz, BMS, and Gilead and travel grants from Jazz, Gilead, and Neovii. The remaining authors declare no conflicts of interest. BNK has received travel support from Kite Gilead and Medac and speaker honoraria from Incyte. He has an advisory role at Kite Gilead.

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Author Contributions

O.P. and D.W. designed research, analyzed data, and wrote the manuscript. P.D., M.S., and W.B. designed research, provided data, and edited the manuscript. The remaining authors provided data. S.A., F.A., B.N.B., G.B., O.K., M.J., G.K., C.K., M.L., S.M., P.G.S., R.S., B.v.T., and V.V. provided data and read and approved the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author upon reasonable request.

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